

Remarks

Reconsideration of this Application is respectfully requested.

I. Status of the Claims

Upon entry of the foregoing amendment, claims 1, 4-7, 22, 23, 25, 26, 54, 57-65, 68-71 and 79-101 are pending in the application, with claim 1 being the independent claim. Claims 2, 3, 11-19, 21, 24, 27-53, 55, 56, 66, 67 and 75-78 were cancelled previously. Claims 8-10, 20 and 72-74 are presently sought to be cancelled without prejudice to or disclaimer of the subject matter therein.

Claims 1, 22, 23, 25, 26, 54, 64, 65 and 79 are sought to be amended. Claims 1, 22, 25, 64 and 79 have been amended to limit the 4*H*-pyrrolo[2,3-*h*]chromenes to those wherein A is an optionally substituted phenyl or pyridyl and by removal of the terms aryl, carbocyclic, heteroaryl and heterocarbocyclic from A, R₃, R₄, Y, and Z. Claims 1, 23, 26, 54, 64, 65 and 79 have been amended to delete the reference to prodrugs. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Examiner Interview on January 16, 2008

Applicants appreciate the courtesy extended by Examiners David K. O'Dell and Rita Desai in an in-person interview held with the undersigned on January 16, 2008, during which all rejections of record and the art cited therein were discussed. Also, Applicants presented data showing unexpected results for the methylated analogs. In

light of the interview, claims 1, 22, 25, 64 and 79 have been amended and claims 8-10, 20 and 72-74 have been cancelled.

III. Rejection of Claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 92, 93 and 95 under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 92, 93 and 95 under 35 U.S.C. § 103(a) as allegedly being unpatentable over PCT Application Pub. No. WO 2001/034591 A2 to Drewe *et al.* (hereinafter "Drewe") or U.S. Patent Appl. No. 11/150,586 (hereinafter "the '586 application") published as U.S. Patent Appl. Pub. No. 2006/035925 A1 to Cai *et al.* or U.S. Patent No. 7,053,117 B2 to Cai *et al.* (hereinafter "the '117 patent") or U.S. Patent No. 7,015,328 B2 to Cai *et al.* (hereinafter "the '328 patent"). Applicants respectfully traverse the rejection.

It is the Examiner's opinion that the cited documents teach compounds that are obvious analogs of the compounds in the present application. (Office Action, pages 13-16). The Examiner states that "it is clear that the prior art differs only in the presence of a methyl group." (Office Action, page 17, line 2). Applicants respectfully traverse this rejection.

Drewe, the '586 application and the '117 patent do not teach the 4*H*-pyrrolo[2,3-*h*]chromenes of the present invention where R₁ is methyl, hydroxymethyl or an ester thereof. However, even assuming *arguendo* that the combination of references did constitute a *prima facie* case of obviousness, this can be overcome by a showing of unexpectedly superior results. *In re Chupp*, 816 F.2d 643, 646 (Fed. Circ. 1987). Applicants respectfully direct the attention of the Examiner to the data set forth in Exhibit A (attached hereto) that was presented during the in-person interview with the Examiners.

Exhibit A directly compares compounds from the as-filed application to compounds disclosed in Drewe, the '586 application and the '117 patent. In Exhibit A, activity measurements in two breast cancer cell lines for the 4*H*-pyrrolo[2,3-*h*]chromenes wherein R₁ = methyl of the as-filed specification (pages 73-75, paragraph [00174], Table I) are compared to activity measurements for 4*H*-pyrrolo[2,3-*h*]chromenes wherein R₁ = H taken from the cited art. As can be seen in Exhibit A, the compounds are very active, with the 4*H*-pyrrolo[2,3-*h*]chromenes wherein R₁ = methyl being two to ten times more potent than those wherein R₁ = H. The activity measurements for a smaller sample of 4*H*-pyrrolo[2,3-*h*]chromenes wherein R₁ = methyl were retested by the inventors and the average of three measurements is presented in Kemnitzer, W., *et al.*, *J. Med. Chem* 51:417-423 (2008)(hereinafter "Kemnitzer")(Exhibit B, attached hereto). As can be seen in Exhibit A, the average measurements presented in Kemnitzer are very similar to those presented in the as-filed specification.

Exhibit A presents a direct comparison of the compounds of the present application with the compounds disclosed in Drewe, the '586 application and the '117 patent and clearly shows definitive and unexpectedly superior results for the compounds of the present application.

Additionally, the '328 patent does not teach the 4*H*-pyrrolo[2,3-*h*]chromenes of the present application. The '328 patent is drawn to compounds wherein the 2-position of the chromene is an oxo or imino group and the chromene contains a double bond between the 3- and 4-positions of the chromene rather than between the 2- and 3-positions of the chromene in the as-filed application.

Therefore, Applicants respectfully request that the rejection of claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 92, 93 and 95 under 35 U.S.C. § 103(a) as allegedly obvious over Drewe, the '586 application, the '117 patent or the '328 patent be withdrawn.

III. Rejection of Claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 92, 93 and 95 based on Nonstatutory Obviousness-type Double Patenting

Claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 92, 93 and 95 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48-51 and 54-81 of co-pending U.S. Patent Appl. No. 10/514,426 (hereinafter "the '426 application") to Cai *et al.* (Office Action, page 19, lines 4-6). Applicants respectfully traverse this rejection.

The Examiner states that the conflicting claims are not identical, but they are "not patently distinct from each other because they cover the same compounds and compositions." (Office Action, page 19, lines 8-9). Applicants respectfully disagree.

The '426 application does not teach the 4*H*-pyrrolo[2,3-*h*]chromenes of the present application. The '426 application is drawn to compounds wherein Z is H, OH, OR₈ or OCOR₈ whereas the claims of the present application are drawn to compounds wherein Z is NR₂₂R₂₃, NHCOR₂₂N(COR₂₃)₂, N(COR₂₂)(COR₂₃), N=CHOR₁₉ or N=CHR₁₉. Therefore, the claims of the '426 application do not recite compounds containing the same Z group.

The Examiner has provided no reason why one would substitute NR₂₂R₂₃, NHCOR₂₂N(COR₂₃)₂, N(COR₂₂)(COR₂₃), N=CHOR₁₉ or N=CHR₁₉ for H, OH, OR₈ or OCOR₈ in the compounds of the '426 application. Therefore, withdrawal of the rejection is respectfully requested.

Claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 92, 93 and 95 are also provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-19, 29, 30, 32, 61 and 57 of co-pending U.S. Patent Appl. No. 11/150,586. (Office Action, page 19, lines 11-13). Applicants respectfully traverse this rejection.

The Examiner states that the conflicting claims are not identical, but they are not patently distinct from each other because they contain the same compounds and compositions. Applicants respectfully disagree.

The compounds recited in the claims of the '586 application all have a hydrogen in the 2-position (corresponding to the Z group in the present claims). In addition, the compounds recited in the claims of the '586 application all have a hydrogen group in the 7-position (corresponding to R₁ in the present claims). The Examiner has provided no reason why one would substitute an amino group for the hydrogen at the 2-position or why one would substitute a methyl, hydroxymethyl or ester thereof for the hydrogen at the 7-position. Additionally, Applicants respectfully direct the attention of the Examiner to the data set forth in Exhibit A for the '586 application. Exhibit A presents a direct comparison of the compositions of the present application with the compounds disclosed in the '586 application and clearly shows definitive and unexpectedly superior results for the compounds of the present application.

Withdrawal of the rejection is respectfully requested.

Claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 92, 93 and 95 are also provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 41-63 and 73-78 of co-pending U.S. Patent Appl. No.

11/072,499 (hereinafter "the '499 application") published as U.S. Patent Appl. Pub. No. 2005/0154015 A1. (Office Action, page 19, lines 18-20). Applicants respectfully traverse this rejection.

The Examiner states that the conflicting claims are not identical, but they are not patently distinct from each other because they contain the same compounds and compositions. Applicants respectfully disagree.

Applicants note that the '499 application is a divisional of U.S. Patent Application No. 09/705,840 which was filed with the same specification and claims as PCT Application Pub. No. WO 2001/034591 (see Section II). However, in the prosecution history for the '499 application, all 4*H*-indolo[4,5-*b*]pyrans were deleted from the application by a preliminary amendment filed with the application. Thus, the claims of the '499 application neither recite the 4*H*-pyrrolo[2,3-*h*]chromenes of the present invention nor do they recite 4*H*-pyrrolo[2,3-*h*]chromenes where R₁ is methyl, hydroxymethyl or an ester thereof. Therefore, the claims of the present application are clearly not obvious in view of the claims of the '499 application.

Withdrawal of the rejection is respectfully requested.

IV. Rejection of Claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 93-96, 99 and 100 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 93-96, 99 and 100 under 35 U.S.C. § 112, first paragraph, as allegedly the specification "while being enabling for certain compound, does not reasonably provide enablement for the protracted list of substituents." (Office Action, page 20, lines 9-11). Applicants respectfully traverse the rejection.

The Examiner alleges that "[t]here is serious reason to doubt the functioning of the scope claimed in the applicant's synthesis. For example, piperdine (sic) is a base and is the catalyst for applicant's ternary condensation reaction, however piperidine is a good nucleophile and when the extremely electron deficient aldehydes of the instant case are employed it would not be unexpected to see Nucleophilic Aromatic Substitution occur." (Office Action, page 21, lines 8-12). The Examiner asserts that numerous examples of nucleophilic aromatic substitution are provided in the literature and reproduces an example from U.S. Patent Appl. Pub. No. 2006/0135505 A1 to Tajimi *et al.*, (hereinafter "Tajimi"). The Examiner also alleges that "the operability of aldehydes like the one required for the synthesis of 40F is remarkable. One would certainly not expect trifluoromethyl or nitro substituted fluoroaldehydes to react in the desired manner." (Office Action, page 22, lines 1-3). Applicants respectfully disagree.

Tajimi teaches the preparation of several tetrahydro-naphthalene derivatives. The example provided by the Examiner, 3-piperidin-1-yl-4-(trifluoromethyl)benzyl amine, was synthesized using 2.2 equivalents of piperidine with heating of the mixture to 55 °C for 43 hours (Tajimi, page 15, paragraph [0205] and [0206]).

In U.S. Patent No. 6,906,203 B1 to Drewe *et al.*, (hereinafter "the '203 patent"), Applicants prepared several chromenes using trifluoromethyl and nitro substituted fluoroaldehyde starting materials as shown in Exhibit C (attached hereto). These compounds were prepared using either *N,N*-diisopropylethylamine as the base or 2.0 equivalents of piperidine at room temperature overnight. In the present application, the same reaction used in the '203 patent is employed using 0.5 to 1.0 equivalents of piperidine at room temperature overnight. Therefore, one having ordinary skill in the art

would expect trifluoromethyl and nitro substituted fluoroaldehydes to react in the desired manner. Additionally, if necessary, a non-nucleophilic base such as *N,N*-diisopropylethylamine can be used instead of piperidine to prevent nucleophilic aromatic substitution from occurring.

The Applicants also assert that the operability of aldehydes like the one required for the synthesis of example 40F is not remarkable. The aldehyde starting material used in the synthesis of example 40F, 3-bromo-4,5-dimethoxybenzaldehyde, is also used to prepare examples 4, 5, 6, 12, 16, 17, 19, 23 and 43 of the present application. Therefore, the synthesis of 40F using 3-bromo-4,5-dimethoxybenzaldehyde would not be considered remarkable to one having ordinary skill in the art.

The Examiner also asserts that the "substituent R1 can have a marked impact on the activity (asserted utility) of the compounds." The Examiner alleges that examples 6 and 19 in Table I of the as-filed specification (pages 73-74, Table I), "show markedly reduced activity compare to (4, 5, 16, 17, 38 and 40F)." (Office Action, page 22, lines 7-8). In an effort to expedite prosecution, claim 1 has been amended to limit the 4*H*-pyrrolo[2,3-*h*]chromenes by removal of the terms aryl, carbocyclic, heteroaryl and heterocarbocyclic from A, R₃, R₄, Y, and Z as suggested by the Examiner during the in-person interview.

The Examiner also alleges that analogs with substitution in the 2-position "are not compounds that function well in applicants desired manner in compounds that differ only in the presence or absence of a ring-fusion by a methylene or methane carbon." (Office Action, page 22, lines 9-11). As mentioned previously, claim 1 has been amended to limit the 4*H*-pyrrolo[2,3-*h*]chromenes by removal of the terms aryl, carbocyclic,

heteroaryl and heterocarbocyclic from A, R₃, R₄, Y and Z as suggested by the Examiner during the in-person interview.

The Examiner also alleges that "the identity of the group in the 4-position is critical for activity" and "it is clear that the long list of groups recited in the claims of the applicant . . . will simply not posses (sic) the desired activity." (Office Action, page 23, line 16, through page 24, line 2). As mentioned previously, claim 1 has been amended to limit the 4*H*-pyrrolo[2,3-*h*]chromenes by removal of the terms aryl, carbocyclic, heteroaryl and heterocarbocyclic from A, R₃, R₄, Y and Z as suggested by the Examiner during the in-person interview.

The Examiner also alleges that "[t]he specification, while being enabling for making salts and certain esters of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds." (Office Action, page 24, lines 5-7). In an effort to expedite prosecution, Applicants have amended claims 1, 20, 23, 26, 64, 65 and 79 to remove the reference to prodrugs.

In view of Applicants' presumptively enabled disclosure, the evidence submitted herewith and the amendments to the claims, Applicants respectfully request that the rejection of claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 93-96, 99 and 100 under 35 U.S.C. § 112, first paragraph, be withdrawn.

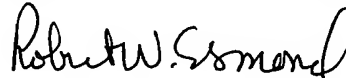
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond
Attorney for Applicants
Registration No. 32,893

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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